CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

TOXICOLOGY STUDY EVALUATION WORKSHEET

I. STUDY IDENTIFICATION

Active Ingredient: Creosote
Chemical Code #: 171 **ID #:** SBC-165854-E
Document #: 50436-031 **Record #:** 153463
EPA Reg. #: 61468 **SB 950 #:** 157
Study Type: Mouse oncogenicity, dermal
Full Study Title: "A 6-month dermal oncogenicity study of creosote in mice"
Company Sponsor: Kopper's Industries, Inc.
Conducting Laboratory: WIL Research Laboratories, Inc.
Final Report Date: 3/7/97 **Project #:** WIL-100005

II. SUMMARY OF WORKSHEET

A. **STUDY STATUS: Is report complete?** yes **Is study acceptable?** yes
Meets EPA guidelines? no **Has useful data?** yes
Major variances from guidelines? Yes. This is a specialized study, requested by U.S. EPA and DPR, and designed to fill remaining data gaps for long-term studies.

B. **CONCLUSIONS: Does this study indicate a possible adverse health effect?** yes
If so, in what area? application site oncogenicity

C. **ONE LINER - Summary of the study:**
**50436-031 153463 Naas, D. J., "A 6-month dermal oncogenicity study of creosote in mice", WIL Research Laboratories, Inc. (Project No. 100005), 3/7/97. Groups of 30 male Crl:CD-1®(ICR)BR mice were dosed in an initiation/promotion study (2 wk initiation, 2 wk rest period, and 26 wk promotion), with materials applied to clipped dorsal skin. Acetone was the carrier and negative control, DMBA (= 9,10-dimethyl-1,2-benzanthracene) was used as the positive initiator, and TPA (12-0-tetradecanoylphorbol-13-acetate) was the positive promotor. Creosote ("North American P1/P13 Creosote CTM", Lot #P1/13-009-A) was used at 3 dose levels, either to evaluate initiation potential (2 weeks of applications, 5 times/week) or promotion potential (applications twice weekly for 26 weeks). Creosote treatments per application were 500 µg/mouse (low dose), 25 mg/mouse (medium dose), or 56 mg/mouse (high dose). Mean mouse body weights were close to 40 g in all groups. Sustained treatment with creosote at the higher two dose levels resulted in 3-6 deaths/group, presumably due to skin damage (erythema, fissuring, eschar, exfoliation) with associated infection and general poor condition. Only lesions of the treatment site and other skin lesions were evaluated for histopathology. Negative control mice had no tumors, and positive controls were functional. Common tumors in positive control and creosote groups were benign papillomas and keratoacanthomas, and malignant tumors such as squamous cell carcinomas (common at higher dose levels) and basal cell carcinomas (uncommon and restricted to higher dose treatments). When creosote was used as an initiator with TPA for promotion, there was no difference between dose levels in numbers of benign tumors (24-27 mice/group with papillomas, 4-7 mice/group with keratoacanthomas), but malignant tumors were limited to 2/group (squamous cell carcinomas) in the higher two creosote groups. When creosote was used as promotor in DMBA-initiated mice, the low dose of creosote yielded only two tumors (papillomas), whereas the medium and high dose creosote groups yielded 20-22 papillomas, 10 to 12 keratoacanthomas, 19-23 squamous cell carcinomas, plus 1

and 2 basal cell carcinomas, respectively. When the high dose creosote level was used for both initiation and promotion phases, tumor yields were 16 papillomas, 4 keratoacanthomas, 26 squamous cell carcinomas, and 2 basal cell carcinomas; indicating that creosote is a "complete" carcinogen. Although creosote was shown to be an effective initiator at all dose levels when coupled with a powerful promotor, the most relevant outcome from this study was a clear dose-response when creosote was evaluated as a promotor. This specialized study fills the oncogenicity data gap, and no further chronic studies are requested at this time. Aldous, 1/8/98.

D. ARE DATA ADEQUATE TO SUPPORT REGISTRATION (if applicable)? yes

Charlie N Aldous — Jan. 8, 1998

Staff Toxicologist — **Date**

1/9/98

III. PROTOCOL SUMMARY

A. ANIMALS, ROUTE OF ADMINISTRATION, AND DURATION OF TREATMENT:

Species: mouse
Strain: Crl:CD-1®(ICR)BR (p.22)
Source of animals: Charles River Laboratories (Portage) (p.22)
Route of administration: dermal application
Vehicle: acetone (p. 21)
Duration of treatment: 30 wk (2 wk initiation, 2 wk no-treatment, 26 wk promotion: p. 21)
Study Dates: 1/31/96 (first treatment) to 8/30/96 (final necropsy) (p. 16)

B. BACKGROUND (including relationship of this study to other studies):

A study of this type had been planned with U.S. EPA, and DPR encouraged production of this study to potentially fill several data gaps for chronic/oncogenicity studies (see Summary of Toxicology Data).

C. TREATMENT LEVELS: (30 male mice in each group: p. 20).

Group	Initiator	Daily Dose	Promotor	Daily Dose
1	(Acetone[1])	N/A	(Acetone)	N/A
2	DMBA[2]	50 µg	(Acetone)	N/A
3	DMBA	50 µg	TPA[3]	5 µg
4	(Acetone)	N/A	TPA	5 µg
5	TPA	5 µg	TPA	5 µg
6	(Acetone)	N/A	DMBA	50 µg
7	Creosote - low	500 µg	TPA	5 µg
8	Creosote - medium	25,000 µg	TPA	5 µg
9	Creosote - high	50 µl, neat[4]	TPA	5 µg
10	DMBA	50 µg	Creosote - low	500 µg
11	DMBA	50 µg	Creosote - medium	25,000 µg
12	DMBA	50 µg	Creosote - high	50 µl, neat
13	Creosote - high	50 µl, neat	Creosote - high	50 µl, neat

[1] Acetone, the diluent in all cases, was applied in 50 µl amounts each treatment. All applications of creosote and positive control substances were likewise 50 µl.

[2] DMBA = 9,10-dimethyl-1,2-benzanthracene, purity minimum 98% by TLC, was used as the positive initiator (p. 17).

[3] TPA (12-0-tetradecanoylphorbol-13-acetate), purity approximately 99%, was used as the positive promotor (p. 17).

[4] Specific gravity of neat (undiluted) creosote was determined to be 1.119 (p. 1425), hence the high concentration delivered about 56 mg per treatment.

IV. STUDY DESIGN AND CONDUCT EVALUATION

A. STUDY PROCEDURES AND REMARKS (e.g., OK, specific parameters; asterisks denote deficiencies, NA indicates not applicable or no comment).

1. **Test article (assay, purity, lot #, stability):** Test article was "North American P1/P13 Creosote CTM", Lot #P1/13-009-A (p. 17). Assays of the technical material before and after the study indicated no loss of stability (p. 1401). OK.
2. **Analysis of dosing material (stability, homogeneity, compound content):** Homogeneity of the lower two dose levels of creosote (the high dose being undiluted and presumed homogeneous) was demonstrated (p. 1408). Creosote was stable over 15 days under refrigeration at 10 and 500 mg/ml (concentrations used for low and medium dose levels: p. 1409). Concentration analyses were generally done at 2-wk intervals, and usually indicated within 10% of target (pp. 1410 ff). Since creosote is a mixture of constituents, the assay technique evaluated 9 such constituents against an internal standard (p. 1401).

3. **Animal selection (species, strain, age, sex):** OK.
4. **Animal husbandry (housing, etc):** Individual caging, PMI Feeds, Inc.© Certified Rodent LabDiet© 5002, standard environmental conditions (p. 23): all OK.
5. **Mortality (and intercurrent disease):** The highest mortality was 12/30 deaths in the acetone/DMBA group. Some groups, including the acetone/acetone group, had no premature deaths. The decedents almost all had mass(es) on the application site, and many had "matting, scabbing, and thickening" on application sites, as well as frequently enlarged spleens or enlarged lymph nodes (p. 35). The deaths appear to be natural consequences of treatment, and not an indication of management problems. OK.
6. **Number of animals (start and termination):** OK
7. **Randomization of animals:** Blocked by body weight (p. 24). OK.
8. **Dose level selection (number of groups and justification):** Initially it was anticipated that creosote formulations would be 100%, 50% (w/v), and 25% (w/v). Since the 25% (w/v) dilution produced skin irritation in the pilot study, the low dose was reduced to 1% (w/v), as indicated in the table above (p. 19). Selected dose levels proved useful for purposes of study. OK.
9. **Route of administration (appropriate for test article):** This study was sought by U.S. EPA at least as early as 1987 (see any past Summary of Toxicology Data), and methods were undoubtedly a cooperative effort of that agency and the registrants. Mouse skin painting studies have been conducted for several decades, providing a solid data base for the test animal. Skin is the most likely route of exposure. OK.
10. **Exposure conditions (schedule and methods):** This study varied dose levels of creosote, and tested creosote both as initiator and promotor, in conjunction with appropriate positive controls. Methods were as follows (from pp. 20-21):
    Application techniques: Mice were shaved about 48 hr before dosing, and once weekly during the study (always at least 18 hr before the next dosing). Investigators were careful to avoid abrasion of skin.

    Initiation:

    DMBA as initiator positive control: one application on study day 11
    Acetone as negative control: one application on study day 11
    Creosote (any dose level): applications for 5 consecutive days during each of the two first weeks of the study. TPA was administered on the same schedule.

    (There was a 2 week period without treatments for all groups after the initiation phase).

    Promotion:

    Twice weekly applications for 26 weeks. OK.
11. **Controls (negative and positive):** OK.
12. **Observations (cageside, body weight, physicals, etc):** Mortality checks were usually done twice daily. Detailed physical exams were done weekly. Once daily, mice were examined for overt toxicity (p. 24). Skin conditions (as erythema and edema) were graded weekly on the four-step Draize system. Masses were evaluated weekly on the application site and elsewhere. OK.
13. **Hematology (appropriate parameters and intervals):** N/A
14. **Serum chemistry (appropriate parameters and intervals):** N/A
15. **Urinalysis (appropriate parameters and intervals):** N/A
16. **Ophthalmology:** N/A
17. **Necropsies (required animals, tissues, or parameters):** A general necropsy was performed on each mouse (p. 26). OK.
18. **Histopathology (tissues, groups, and number of animals):** Nearly all tissues commonly evaluated in chronic studies were preserved in formalin (pp. 26-27). These tissues were processed and stained (H&E), however the only tissues systematically

examined were skin sections from the application site and any masses identified grossly (pp. 27-28).
Justification of method: The mouse skin application model is well-studied, and allows for separation of stages of neoplastic processes. Further, positive mouse skin carcinogenicity responses are considered to be indicative of general oncogenicity risk to humans (see Rice, R. H. and D. E. Cohen in Casarett & Doull's Toxicology: The Basic Science of Poisons, 5th Edition, Klaassen, C.D., Editor, McGraw-Hill, New York, 1996, p. 543). A WHO monograph prepared in January of 1985 (referenced in Summary of Toxicology Data as Record No. 132720) noted that there is "sufficient evidence" that **coal-tar** is carcinogenic in humans (causal association with skin cancer). Further, "there is 'limited evidence' that **coal-tar-derived creosotes** are carcinogenic in humans". The Creosote Summary of Toxicology Data cites several positive studies showing tumors in mice, usually at the site of skin application, but also including lung tumors (see especially Record No. 055552). The present study was conducted to obtain some qualitative information (as the relative importance of creosote as initiator or promotor) and dose-response data in the mouse skin application system. OK.

19. **Appropriateness of methods:** (see #18, above)
20. **Treatment of results (data summarization and statistics):** OK
21. **Study report (complete, reflects data, data cited but missing):** OK
22. **Consistency (with other studies of this type):** OK
23. **Good laboratory practice (internal audits, sign-offs):** OK (see pp. 45-46 for QA).

V. RESULTS

A. EFFECTS REPORTED:

Below are summary data for essential findings of the report. Note that "Group No." in the cited tables identify "Computer Group No.", whereas the "Study Group No." is used consistently throughout in this review. For reference, the respective treatment designations are provided (from p. 20 of report). Note that "Study Group Nos." 5 and 6 are tabulated separately from the other groups: these are the two least essential groups, since they do not test creosote, nor are they true positive or negative controls. Report data tables use descriptors (such as "DMBA/Acetone") to eliminate confusion.

Study Group Designations

Study Group No.	Computer Group No.	Initiator	Promotor
1	1	(Acetone)	(Acetone)
2	2	DMBA	(Acetone)
3	3	DMBA	TPA
4	4	(Acetone)	TPA
5	1	TPA	TPA
6	2	(Acetone)	DMBA
7	5	Creosote - low*	TPA
8	6	Creosote - medium	TPA
9	7	Creosote - high	TPA
10	8	DMBA	Creosote - low
11	9	DMBA	Creosote - medium
12	10	DMBA	Creosote - high
13	11	Creosote - high	Creosote - high

* Creosote levels are abbreviated in the following table as "Creo-Lo", "Creo-M", and "Creo-Hi"

Deaths noted in the table below all occurred during the promotion phase, and were usually restricted to the last third of the study. The group with DMBA during the promotion phase (note that DMBA is a standard inducer, and not designated as a promotor) had the highest mortality, beginning as early as study week 14 (i.e. promotion week 10).

Clinical signs were comparatively minor during the initiation phase, aside from a general increase in yellow material in the urogenital area in the high dose creosote groups compared to other groups (p. 64, not tabulated below). Similar findings were noted in the longer promotion phase, as shown in the table below.

Non-application tumor site data (pp. 100 ff.) did not find any increases in tumors of Groups 12 and 13 (the two groups with the highest creosote exposures) as compared with concurrent controls. There does not appear to be any need to evaluate non-site tumors in this study.

Body weight data were comparatively uneventful, aside from a transient reduction in the Creo-Hi/Creo-Hi group (Study Group #13), and a more consistent reduction in the Acetone/DMBA group (pp. 106, 113 ff). Food consumption was commonly higher in the majority of treated groups compared to concurrent controls (pp. 134 ff).

Numbers of Mice per Group Affected With Noteworthy Observations

Observation (pages cited)	Study Group Number												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Initiation Phase Treatment	Acetone	DMBA	DMBA	Acetone	TPA	Acetone	Creo-Lo	Creo-M	Creo-Hi	DMBA	DMBA	DMBA	Creo-Hi
Promotion Phase Treatment	Acetone	Acetone	TPA	TPA	TPA	DMBA	TPA	TPA	TPA	Creo-Lo	Creo-M	Creo-Hi	Creo-Hi
# Mice Assigned to Study	(30)	(30)	(30)	(30)	(30)	(30)	(30)	(30)	(30)	(30)	(30)	(30)	(30)
# Mice Not Surviving (52, 58)	0	1	0	1	0	12	0	0	0	0	3	6	3
Clinical Signs: (57 ff.) Promotion Phase, from Weekly Clinical Exams													
Dehydration	1	1	5	5	1	18	3	2	3	2	7	9	14
Hair Loss													
Forelimbs	1	2	2	3	1	3	3	3	1	0	6	16	18
Ventral Trunk	0	0	0	1	2	14	4	1	0	0	4	27	25
Urogenital Area	0	0	0	0	0	0	0	0	0	0	3	10	11
Dried yellow material													
Urogenital Area	8	7	11	7	7	22	7	8	21	4	21	24	25
Ventral Trunk	3	2	6	2	2	16	3	5	6	2	11	16	14
Anogenital Area	4	1	5	3	2	17	1	3	0	2	7	14	13
Dermal Observations: Initiation Phase (94 ff.)													
Erythema													
Very Slight	0	5	3	0	16	0	19	12	1	4	7	4	6
Slight	0	0	0	0	16	0	0	16	9	0	0	0	12
Moderate	0	0	0	0	3	0	0	7	3	0	0	0	0
Severe	0	0	0	0	15	0	0	24	29	0	0	0	27
Edema													
Very Slight	0	0	0	0	19	0	0	18	16	0	0	0	26
Slight	0	0	0	0	4	0	0	12	11	0	0	0	20
Moderate	0	0	0	0	0	0	0	10	10	0	0	0	4
Severe	0	0	0	0	0	0	0	0	2	0	0	0	1
Fissuring	0	0	0	0	0	0	0	0	8	0	0	0	3
Desquamation	0	14	23	1	30	0	30	30	30	20	23	22	30
Eschar	0	0	0	0	13	0	0	23	29	0	0	0	27
Exfoliation	0	0	0	0	3	0	0	8	25	0	0	0	19
Residual Test Material Within Application Site	0	0	0	0	0	0	5	30	30	0	0	0	30

Observation (pages cited)	Study Group Number												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Initiation Phase Treatment	Acetone	DMBA	DMBA	Acetone	TPA	Acetone	Creo-Lo	Creo-M	Creo-Hi	DMBA	DMBA	DMBA	Creo-Hi
Promotion Phase Treatment	Acetone	Acetone	TPA	TPA	TPA	DMBA	TPA	TPA	TPA	Creo-Lo	Creo-M	Creo-Hi	Creo-Hi
Dermal Observations: Promotion Phase (96 ff.)													
Erythema													
Very Slight	0	0	27	24	28	24	28	29	29	2	29	26	28
Slight	0	0	29	28	29	19	26	23	24	1	29	30	28
Moderate	0	0	1	3	1	7	0	0	0	0	2	2	2
Severe	0	0	19	22	21	30	20	15	20	1	29	30	30
Edema													
Very Slight	0	0	30	30	30	30	30	29	30	3	30	30	30
Slight	0	0	24	29	27	30	27	23	26	0	29	29	26
Moderate	0	0	5	8	3	3	3	2	2	0	5	5	3
Severe	0	0	1	0	0	1	0	0	0	0	0	0	0
Fissuring	0	0	11	15	14	23	9	8	8	0	13	12	13
Desquamation	0	12	30	30	30	30	30	30	30	30	30	30	30
Eschar	0	0	19	22	21	30	20	15	20	1	29	30	30
Exfoliation	0	0	6	13	11	21	4	2	7	1	8	11	8
Residual Test Material Within Application Site	0	0	0	0	0	0	0	0	0	9	30	30	30
Clear Exudate	0	0	12	12	11	27	7	4	6	0	16	16	26
Mass Incidence Data (at application site)													
# with Masses	0	0	30	0	9	29	30	30	30	4	29	30	30
# with Multiple Masses	0	0	29	0	3	29	28	28	29	1	29	30	30
Mean # Masses/Mouse	0	0	13	0	3	13	7	10	10	1	10	13	11
Mean Days to First Mass	0	0	67	0	162	84	91	71	60	157	115	109	95
Gross Findings at Planned Necropsy (other than external surfaces reported above in clinical observations) (154 ff.)													
# Term Survivors	30	29	30	29	30	18	30	30	30	30	27	24	27
Lung Nodules	0	0	0	0	0	0	0	0	0	0	0	0	4
Spleen Enlarged	0	1	7	4	1	13	3	3	6	0	14	14	16

Observation (pages cited)	Study Group Number												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Initiation Phase Treatment	Acetone	DMBA	DMBA	Acetone	TPA	Acetone	Creo-Lo	Creo-M	Creo-Hi	DMBA	DMBA	DMBA	Creo-Hi
Promotion Phase Treatment	Acetone	Acetone	TPA	TPA	TPA	DMBA	TPA	TPA	TPA	Creo-Lo	Creo-M	Creo-Hi	Creo-Hi
Lymph Node Enlarged:													
Axillary	0	0	2	0	1	8	3	2	2	0	6	7	9
Scapular	0	0	0	0	0	0	0	1	1	0	6	6	8
Dark Red Contents													
Duodenum	0	0	0	0	0	3	0	0	0	0	0	0	1
Ileum	0	0	0	0	0	3	0	0	0	0	2	1	0
Jejunum	0	0	0	0	0	4	0	0	0	0	1	2	1
Stomach	0	0	0	0	0	4	0	0	0	0	1	4	1
Histopathology, Treated Skin, Survivors (168 ff.) N=	30	29	30	29	30	18	30	30	30	30	27	24	27
Epithelial Hyperplasia	0	0	16	20	9	9	24	23	15	2	22	10	18
Inflammation, acute	0	0	8	17	1	8	17	12	12	1	18	10	17
Ulceration	0	0	7	11	0	0	7	3	5	0	10	4	6
Hyperkeratosis	0	0	0	0	0	0	0	0	0	0	0	0	5
Masses, All Mice (p. 180)													
Papilloma	0	0	27	0	4	24	27	24	26	2	23	25	16
Keratoacanthoma	0	0	4	0	0	15	4	7	7	0	14	11	4
Squamous Cell Carcinoma	0	0	4	0	0	18	0	2	2	0	21	29	28
Basal Cell Carcinoma	0	0	0	0	0	1	0	0	0	0	1	3	2
Lymphoma	0	0	0	0	0	3	0	0	0	0	0	0	2

B. NO OBSERVED EFFECT LEVEL (NOEL): N/A (not the primary purpose of study)

VI. DISCUSSION

A. MAJOR DEFICIENCIES (if present). What are they and can they be corrected with additional information? Be specific: This study is quite different in many ways from a standard oncogenicity study, but the design was a cooperative effort between the registrant and U.S. EPA, and had been determined by DPR to address remaining long-term study requirements, if properly executed. The study achieves its intended purposes and is acceptable as presented.

CCQ

B. DISCUSSION OF RESULTS (if necessary). Were there possible adverse health effects? Are there any recommendations specific to this study?

This study was designed to evaluate creosote as a tumor initiator and/or promotor, and to provide dose-response information for both phases of tumor development. Individual data (Parts 4-8) show that the great majority of grossly evident tumors following standard necropsy procedures arose in the treatment site, as expected from creosote studies previously evaluated (see Summary of Toxicology Data). The only exception appears to be lung lesions. The four grossly evident lung nodules were exclusively in Group 13 (high dose creosote as initiator and promotor) and could have represented a non-site tumor etiology (consistent with Record No. 055552 in the Summary of Toxicology Data). Lung was not a protocol tissue for histopathology in this study. Given the comparative sensitivity of application sites to relevant tumors under conditions of this study, it is clear that the protocol decision to focus on skin lesions was a valid choice.

Clinical sign and morbidity data were consistent with non-neoplastic dermal responses in the mice. Each of the positive control substances and creosote markedly increased skin lesions such as erythema and eschar, however DMBA and the two higher dose levels of creosote caused the highest incidences and/or severities when used during the promotion phase of the study. These four groups accounted for almost all of the mortalities in the study. Individual data for non-survivors (the first portion of Part 4) do not indicate "cause of death", however the presence of dehydration, hair loss, and yellow-stained fur was preferentially elevated in these groups, and suggests that morbidity arose as a result of reduced general condition in most cases. Gross findings, particularly enlarged spleen and enlargement of the lymph nodes serving the treatment site, also appear to be consistent with irritation, inflammation, and/or infection as major factors in the demise of these mice.

Of the five tumor types included in the above table, papillomas, keratoacanthomas, and squamous cell carcinomas appear most relevant for further evaluation. Relevant tumor responses were absent after treatments with acetone only, with DMBA/acetone, and with acetone/TPA.

The presence of 4 papillomas following 2 weeks of intensive treatment with TPA during the initiation phase followed by bi-weekly exposures of TPA during the promotion phase showed that this "promotor" could elicit some response without benefit of an "initiator".

There were 2 papillomas in the DMBA/(low dose creosote) group, indicating a modest promotor capability of creosote following 500 µg bi-weekly exposures. Promotion with the higher creosote levels (25 to 56 mg/treatment) yielded substantial numbers of papillomas, keratoacanthomas, and squamous cell carcinomas in DMBA-initiated rats, without a dose-response evident in the higher dose range.

Creosote was an effective initiator at all dose levels tested. Only benign tumors (papillomas and keratoacanthomas) arose after initiation with 500 µg exposures of creosote. Much higher exposure levels of creosote for initiation (treatments of 25 to 56 mg/day) made very little difference in the incidences of benign tumors. The latter dose groups yielded 2/30 mice each with squamous cell carcinoma.

Creosote was considered to be a "complete" carcinogen in this study, since the high dose (56 mg/treatment), when used for initiation and promotion stages, led to a high yield of benign and malignant tumors. Study design did not include a series of creosote dose levels in the absence of DMBA or TPA.

Creosote was noted to leave "residual test material within application site" in all mice at medium and high dose levels, and in many low dose mice. This may account in part for the lack of a clear dose-response, since actual exposure may not have risen proportionately with dose levels.

Perhaps the weakest aspect of this study is that it does not provide a NOEL for creosote in the presence of a potent promotor such as TPA. While this is unfortunate, anticipated creosote exposure scenarios would not be coupled with such promotor exposures. The very low level of tumor response in Study Group 10 (DMBA/(low dose creosote) provides an effective dose-response curve for sustained creosote exposures. It is probably better to use these data than those of older studies, despite the confounding effect of DMBA, because the creosote used was selected to represent currently used technical.

Creosote P1/P13 blend: 2-Generation Reproduction Toxicity in Rats
Creosote Council II. 1995. MRID No. not available.